Translation

PCT/DE2003/002799

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 510471 AJG/apb	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE2003/002799	International filing date (*day/month/year*) 22 August 2003 (22.08.2003)	Priority date (*day/month/year*) 30 August 2002 (30.08.2002)
International Patent Classification (IPC) or national classification and IPC C12P 7/62		
Applicant MASSEY UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 March 2004 (29.03.2004)	10 December 2004 (10.12.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE2003/002799

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-28, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-29, filed with the letter of 31 March 2004 (31.03.2004)

☒ the drawings:
pages 1/7-7/7, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, Nos. 30-35

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-29	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-29	NO
Industrial applicability (IA)	Claims	1-29	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: Madison L.L. & Huisman G.W., Microbiology and Molecular Biology Reviews, American Society for Microbiology, US (03-1999), 63(1), 21-53

D2: US-A-6022729, 08.02.2000

D3: Steinbüchl A. & Füchtenbusch B.: Trends in Biotechnology, Elsevier Publications, Cambridge, GB (01-10-1998), 16(10), 419-427

D4: US-A-6146665, 14.11.2000

D5: WO-A-9920256, 29.04.1999

1 **Amendments** (PCT Article 28(2))

An amended set of claims was submitted with the letter of 30 March 2004, received on 31 March 2004. The new claims 12 and 13 are now dependent on all the preceding claims. Said new claims 12 and 13 are based on claims 17 and 18 as originally filed, which depended on claims 1 and 2 as originally filed, the latter corresponding to the present claim 1. The additional dependence on claims 2-11 leads to specific combinations of technical features which do not follow directly and clearly from the application

as originally filed or are not comprised by the content thereof, in consequence of which these amendments are not allowable according to PCT Article 28(2)). Therefore, claims 12 and 13 as originally filed have been examined.

The remaining amendments correspond to the requirements of PCT Article 28(2)).

2 **Novelty** (PCT Article 33(2))

The subject matter of claims 1-29 appears to be novel as per PCT Article 33(2) in light of the prior art.

3 **Inventive step** (PCT Article 33(3))

3.1 D1, which is considered to represent the closest prior art, discloses processes for preparing polymeric particles from polyhydroxyalkanoates (PHAs) synthesized *inter alia* in *Ralstonia eutropha* and *Escherichia coli* (pages 37 and 42) using genes from the PHA biosynthetic pathway (pages 26-29), wherein fatty acids and other hydrocarbons (including those with functional side groups) may be used as substrates (pages 30-33). Further, D1 discloses that particle size is determined by the amount of particle-binding proteins present, including phasins (phaP) and PHA polymerase (=PHA synthase), since phasin overexpression leads to an increased number of small particles, and that the molecular weight of the polymer is determined by the ratio of substrate to enzyme: that is, that the amount of substrate exerts a contributory influence on particle size (pages 29-30). In light of D2, in

which a phasin is likewise coexpressed and particles having a diameter of between 200 and 500 nm are produced (column 12), particle size may be considered implicitly to lie in the range indicated in the present application.

3.2 The subject matter of the new claims 1-9, 11-13 and 24-27 differs from the said closest prior art in that the genes which are introduced code for fusion proteins comprising a particle-binding domain and a binding domain, the latter domain being able to bind to bioactive substances or coupling reagents. The technical effect of this difference is manifested in particle functionalization: that is, the particles are able to bind to (for example) bioactive substances and thus to serve as vehicles therefor.

The problem addressed by the present invention is therefore that of providing particles that are suitable for transporting bioactive substances.

3.3 Since D1-D5 all describe PHA particles or polymeric nanoparticles, a person skilled in the art would recognize them all to be relevant and readily combine them in order to solve the problem of interest.

D2 discloses that PHA particles are enveloped in a layer of lipids and proteins and that other proteins, comprising a particle binding domain, may be immobilized on such particles (columns 4, 12 and 19). This known ability to immobilize proteins on particles would immediately suggest to a person skilled in the art the possibility of immobilizing a bioactive substance or a coupling reagent and

consequently the subject matter of the new claims 1-9, 11-13 and 24-27, in the absence of, for example, a surprising technical effect, represents an obvious variation on the prior art (EPC Article 56) since, instead of being encapsulated in the particle (a well-known practice in the prior art: cf., e.g., D4), an active substance that is to be transported is bound only on the particle surface.

3.4 D3 likewise discloses PHA production by, *inter alia*, *Ralstonia eutropha* and the corresponding biosynthetic genes with the use of fatty acids (also having various substituents) as a substrate, likewise in relation to *in vitro* synthesis using isolated enzymes (page 424). The obvious combination of D3 and D1 renders claims 14-21 obvious and they therefore lack inventive step as per EPC Article 56.

3.5 The remaining claims pertain to exchange of the lipid layer enveloping the particles (claims 10 and 23) and use of the particles in preparing drugs (claims 22 and 28) for treating diseases of the central nervous system (claim 29).

3.5.1 Since it is well known that targeting is a general problem in drug delivery and that a lipid layer with embedded proteins plays an important role in targeted drug delivery, the subject matter of claims 10 and 23 represents an obvious variation on the prior art and, in the absence of, for example, a surprising technical effect, cannot, therefore, substantiate inventive step as per EPC Article 56.

3.5.2 D4 additionally discloses the use of PHA particles to transport drugs (column 4, figure 2). The subject

matter of claims 22 and 28 consequently lacks inventive step as per EPC Article 56.

3.5.3 D5 additionally discloses the concept of using carrier particles (including polymeric nanoparticles) to transport drugs across the blood-brain barrier to the central nervous system. Consequently, the subject matter of claim 29 represents an obvious variation on the prior art and cannot, therefore, substantiate inventive step as per EPC Article 56.

4 **Clarity** (PCT Article 6)

4.1 Claims 1, 6, 11, 14, 16 and 21 do not meet the requirements of PCT Article 6 because the subject matter for which protection is sought is not clearly defined. The claims attempt to define the subject matter in terms of the result to be achieved, but in doing so merely state the problem to be solved without showing the technical features required to achieve this result.

4.2 In the first subordinate clause of claim 26, a verb is missing ("..., in die... ?") ["..., in which... ?"], in consequence of which the claim is unclear (PCT Article 6).

4.3 The word "Anspruch" ["claim"] in claim 13 is redundant.